

PATENT COOPERATION T. TY

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
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in its capacity as elected Office

Date of mailing (day/month/year) 25 April 2000 (25.04.00)	
International application No. PCT/GB98/02952	Applicant's or agent's file reference M98/0404/PCT
International filing date (day/month/year) 01 October 1998 (01.10.98)	Priority date (day/month/year) 28 August 1998 (28.08.98)
Applicant WANG, Wei et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
22 March 2000 (22.03.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>Olivia RANAIVOJAONA</p> <p>Telephone No.: (41-22) 338.83.38</p>
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

McNeight & Lawrence
Regent House, Heaton Lane
Stockport, Cheshire, SK4 IBS
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year)

26. 10. 00

Applicant's or agent's file reference

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IMPORTANT NOTIFICATION

International application No.
PCT/GB98/02952

International filing date (day/month/year)
01/10/1998

Priority date (day/month/year)
28/08/1998

Applicant

DE MONTFORT UNIVERSITY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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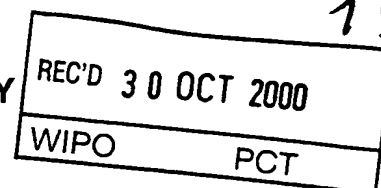
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ./.	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB98/02952	International filing date (day/month/year) 01/10/1998	Priority date (day/month/year) 28/08/1998	
International Patent Classification (IPC) or national classification and IPC A61B5/05			
Applicant DE MONTFORT UNIVERSITY et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 22/03/2000	Date of completion of this report 26. 10. 00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stern, M Telephone No. +49 89 2399 2239

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/02952

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-18 as originally filed

Claims, No.:

1-28 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/02952

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-7, 9, 12-14, 18-21, 23, 26-28
	No:	Claims	1-3, 8, 10, 11, 15-17, 22, 24, 25
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4-7, 9, 12-14, 18-21, 23, 26-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Regarding Section V:

1. Of the documents cited in the international search report, the following will be addressed in the present report:

D1: Jossinet J: "Variability of impedivity in normal and pathological breast tissue"; Medical and Biological Engineering and Computing, Vol. 34, No. 5, Sept. 1996, pages 346-350.

Document D1 makes reference at the bottom of the left column of page 348 to the following document:

D2: Surowiec A.J. et al.: "Properties of Breast Carcinoma and the Surrounding Tissues"; IEEE Transactions on Biomedical Engineering, Vol. 35, No. 4, April 1988, pages 257-263

2. Claims 1-3, 8, 10 and 11 do not satisfy the novelty requirement of Art. 33(2) PCT for the following reasons:

(i) Both documents D1 and D2 anticipate the apparatus of claims 1-3 in that they define an apparatus with an electrode arrangement for measuring and processing electrical impedance properties of bodily matter for correlating the detected properties with breast cancer, the apparatus using electrical signals of a frequency greater than 1 MHz; see in D1, the abstract and the paragraph bridging the two columns of page 348; see in D2, the abstract and Figs. 3 and 4.

(ii) D1 explicitly mentions (cf last sentence of the abstract; section 4.1 in D1) that the detected impedance information is related to dispersion frequencies, as defined in claim 8.

(iii) Comparisons with different bodily matter, in particular fatty tissue in the breast, as defined in claims 10 and 11, is known from D1 (cf paragraph bridging the two column of page 347).

3. Claims 4-7, 9 and 12-14 do not satisfy the requirement of inventive step according to Art. 33(3) PCT for the following reasons:

(i) The detection of different stages of a carcinoma, as recited in claims 4-6, is a task which the skilled person using the apparatuses of either D1 or D2 would naturally attempt. In particular, D2 even suggests the detection of various stages of the tumour development in the sentence bridging pages 259 and 260.

(ii) The different processing models vaguely defined in claims 7 and 9 (see Section VIII below), as well as the electrode placement choice of claim 14, would readily be envisioned by a skilled person upon taking notice of the disclosures of D1 and D2.

(iii) The comparison of detected data with a database, especially from subjects of differing and known ages, as defined in claims 12 and 13, is an obvious technique to determine cancerous abnormalities in tissue.

4. Method claims 15-28 are entirely analogous to the aforementioned apparatus claims. Hence, for the reasons given above, *mutatis mutandis*, claims 15-17, 22, 24 and 25 do not satisfy the requirement of Art. 33(2) PCT, and claims 18-21, 23 and 26-28 do not satisfy the requirement of Art. 33(3) PCT.

Regarding Section VII:

1. To meet the requirements of Rule 6.3(b) PCT the independent claim should have been properly cast in the two part form, with those features which in combination are known from D1 being placed in the preamble.
2. Reference signs in parentheses should have been inserted in the claims to increase their intelligibility, Rule 6.2(b) PCT. This applies to both the preamble and characterising portion.
3. To meet the requirements of Rule 5.1(a)(ii) PCT, document D1 should have been cited in the description and the relevant background art disclosed therein should

have been briefly discussed.

Regarding Section VIII:

1. The following clarity objections should also have been remedied (Art. 6 PCT):

(i) In claim 1, the term "abnormalities" is vague and of relative and subjective nature. It should have been replaced by the term "carcinoma", as in claim 2.

(ii) The expression "fractal model of tissue impedance" in claim 7 is of uncertain meaning and should have been clarified according to the meaning the applicant intends to provide the expression with (cf page 12, second paragraph).

(iii) In claim 9, it should have been made clear that the intra and extra cellular impedances are the detected impedance properties of claim 1.

(iv) The term "referencing" in claims 10 and 11 is vague and obscure.

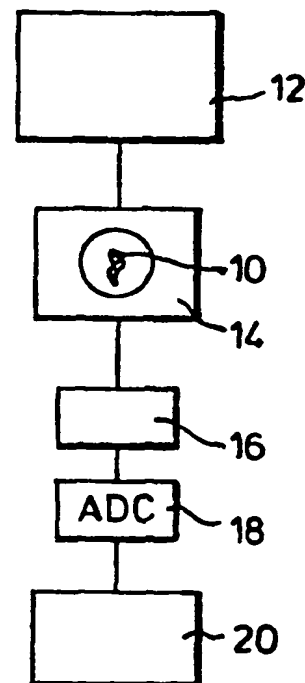
(v) Claim 14 seems to recite only a method step, and does not clearly limit the recited apparatus.

(vi) The corresponding method claims would have needed analogous amendments.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61B 5/05	A1	(11) International Publication Number: WO 00/12005 (43) International Publication Date: 9 March 2000 (09.03.00)
(21) International Application Number: PCT/GB98/02952 (22) International Filing Date: 1 October 1998 (01.10.98) (30) Priority Data: 9818790.9 28 August 1998 (28.08.98) GB (71) Applicant (for all designated States except US): DE MONT-FORT UNIVERSITY [GB/GB]; The Gateway, Leicester LE1 9BH (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): WANG, Wei [CN/GB]; 23 Fairstone Hill, Oadby, Leicester LE2 5RL (GB). McCORMICK, Malcolm [GB/GB]; 125 Knowle Lane, Sheffield S11 9SN (GB). (74) Agents: McNEIGHT, David, Leslie et al.; McNeight & Lawrence, Regent House, Heaton Lane, Stockport, Cheshire SK4 1BS (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: APPARATUS AND METHOD FOR DETECTING ABNORMALITIES IN BODILY MATTER		
(57) Abstract There is disclosed electrical impedance tomography apparatus adapted to detect abnormalities in bodily matter comprising: electrical signal generating means for generating electrical signals at a plurality of frequencies; an electrode arrangement for applying the electrical signals to the bodily matter and detecting electrical impedance properties of the bodily matter; and data processing means for correlating the detected electrical impedance properties with the presence or absence of abnormalities in the bodily matter; in which electrical signals of a frequency greater than 1 MHz, preferably greater than 2 MHz, more preferably greater than 3 MHz and most preferably greater than 4 MHz are applied to the bodily matter.		



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Apparatus and Method for Detecting
Abnormalities in Bodily Matter

This invention relates to an apparatus and method for detecting abnormalities in bodily matter, with particular, but by no means exclusive, reference to the detection of breast carcinomas.

Breast cancer is a major cause of mortality in Western countries. In the UK, one in twelve women develop this condition during their lifetime.

Conventionally, screening for breast cancer has employed x-ray mammography. The x-ray images produced thereby are analysed by eye to determine whether any abnormalities are present. Should a potential abnormality be located, further analysis by surgery typically a tissue biopsy, is usually required. Clearly, a non-invasive alternative procedure for investigating breast lesions would be highly desirable. Other disadvantages with x-ray mammography are that ionising radiation is employed, and that identification of lesions from the x-ray image requires a background comprising a substantially contrasting material. As a result, the ability of x-ray mammography to identify low radio-density tumours, and tumours in younger woman, is limited. A further and highly significant disadvantage is that a tumour must be relatively large (for example at least 5 millimetres) before detection is possible with X-ray mammography.

Electrical impedance tomography (EIT) is a well known technique which provides 2 dimensional images or "slices" through an object using an array of electrodes which typically encircle the object. The images are obtained by applying current to the object via selected electrodes, and detecting the potentials generated at other electrodes in the array. The measured potentials depend on the electrical impedance of the object and from these data it is possible to perform a back projection technique to construct an

image of the electrical impedance of the objects. By performing a plurality of such measurements, both 2- and 3-dimensional image can be assembled.

Dijkstra et al (A. M. Dijkstra, B. H. Brown, A. D. Leathlard, N. D. Harris, D. C. Barber and D. L. Edbrooke; Journal of Medical Engineering & Technology, 17 (1993) 89-98) provides an overview of clinical applications of EIT. Images may be static or dynamic, i.e., representing changes in impedance of the subject over a period of time, an example being an image of the thorax during breathing. It is noted in Dijkstra et al that EIT produces images of body function and not high quality anatomical images. Elsewhere in Dijkstra et al it is commented that static images are technically difficult to produce and that there is no clinical experience with static EIT images. Thus, the teaching of Dijkstra et al is towards the production of dynamic images of body function, and away from the analysis of specific abnormalities, such as carcinomas, via static EIT.

The present invention is concerned with an improved EIT technique which enables non-invasive detection and imaging of abnormalities in bodily matter, a primary, but non-limiting, example of which is the detection and imaging of breast carcinomas.

According to a first aspect of the invention there is provided electrical impedance tomography apparatus adapted to detect abnormalities in bodily matter comprising:

electrical signal generating means for generating electrical signals at a plurality of frequencies;

an electrode arrangement for applying the electrical signals to the bodily matter and detecting electrical impedance properties of the bodily matter; and

data processing means for correlating the detected electrical impedance properties with the presence or absence of abnormalities in bodily matter;

in which electrical signals of a frequency greater than 1 MHz, preferably greater than 2 MHz, more preferably greater than 3 MHz and most preferably greater than 4 MHz, for example 5 MHz, are applied to the bodily matter.

At such high applied frequencies, differences between normal tissue and abnormal tissue are more pronounced, permitting the detection of abnormalities by EIT.

The apparatus may be adapted to detect a carcinoma, which may be a breast carcinoma. In contrast to x-ray mammography, ionising radiation is not employed, and the technique may be successfully applied to younger women and/or to tumours of low radio-density. Furthermore, it is possible to provide a 3 dimensional image, possibly leading to more accurate determination of the position of a carcinoma.

The apparatus may be adapted to detect a stage 3 carcinoma and/or a stage 2 carcinoma and/or a stage 1 carcinoma. These stages are defined in Tables 1 and 2, below.

The data processing means may correlate the detected electrical impedance properties with the presence or absence of abnormalities using a fractal model of tissue impedance.

Information related to dispersion frequencies may be used to perform the correlation.

The ratio of extra-cellular impedance and intra-cellular impedance may be used to perform the correlation. The ratio of extra-cellular impedance and "membrane" impedance may be used to perform the correlation.

The data processing means may reference the detected electrical impedance properties of the bodily matter to the detected electrical impedance properties of other bodily matter. In the case of breast carcinoma detection, the impedance properties may be referenced to detected electrical impedance properties of fatty tissue or ductal/stroma tissue in the breast.

The data processing means may be adapted to compare the detected electrical impedance properties with a database of impedance properties corresponding to bodily matter of known composition. The database may comprise impedance properties of bodily matter obtained from subjects of differing and known ages, heights, weights or races, or normalised figure.

At least the electrode arrangement may be disposed in a women's brassiere. This permits screening without the physical discomfort associated with x-ray mammography.

According to a second aspect of the invention there is provided an electrical impedance tomographic method for detecting abnormalities in bodily matter comprising the steps of:

generating electrical signals at a plurality of frequencies;

applying said electrical signals to the bodily matter;

detecting electrical impedance properties of the bodily matter; and

correlating the detected impedance properties with the presence or absence of abnormalities in the bodily matter;

in which electrical signals of a frequency greater than 1 MHz, preferably greater than 2 MHz, more preferably greater than 3 MHz and most preferably greater than 4 MHz are applied to the bodily matter.

The abnormality may be a carcinoma, which may be a breast carcinoma.

A stage 3 carcinoma and/or a stage 2 carcinoma and/or and stage 1 carcinoma may be detected.

The correlation of the detected impedance properties with the presence or absence of abnormalities may use a fractal model of tissue impedance.

Information related to dispersion frequencies may be used to perform the correlation.

The ratio of intra-cellular impedance and extra-cellular impedance may be used to perform the correlation. Other ratio smay be used in addition to the extra-cellular vs. intra-cellular impedance. These may include for exmple the intra-cellular impedance divided by the cellular capacitance, which may provide a significant index indicating the abnormality of the tissue. Other ratios which may be used are given in Tables 3-5 (below).

The detection of impedance properties of the bodily matter may be performed at a controlled temperature. The detected electrical impedance properties of the bodily matter may be referenced to detected electrical impedance properties of other bodily matter. In the case of breast carcinoma detection the impedance properties may be referenced to detected electrical impedance properties of other tissues within the breast, for example a normalised response of stroma.

The detected electrical impedance properties may be compared with a database of impedance properties corresponding to bodily matter of known composition. The database may comprise impedance properties of bodily matter obtained from subjects of differing and known ages. The temperature at which readings were obtained and the post-excision age of the bodily matter of the database may also be used in any comparison.

Table 1: TNM classification and staging for breast cancer

Classification	Primary tumour (T)
TX	Primary tumour cannot be assessed
TO	No evidence of primary tumour
Tis	Carcinoma in situ (ductal or lobular or Paget's disease with no tumour)
T1	Tumour 2 cm or less in greatest dimension
T1a	0.5 cm or less in greatest dimension
T1b	More than 0.5 cm but not more than 1 cm in greatest dimension
T1c	More than 1 cm but not more than 2 cm in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour of any size with direct extension to chest wall or skin
T4a	Extension to chest wall
T4b	Edema (including peau d'orange) or ulceration of skin breast or satellite skin nodules confined to same breast
T4c	Both (T4a and T4b)
T4d	Inflammatory carcinoma

	Regional lymph nodes (pathologic pN)
pNX	Regional nodes cannot be assessed
pNO	No regional node metastases
pN1	Metastases to movable ipsilateral axillary nodes
pN1a	Micrometastases only (none larger than 0.2 cm)
pN1b	Metastasis to node(s), any larger than 0.2 cm
pN1bi	Metastasis in 1 to 3 nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
pNbii	Metastasis to 4 or more nodes, any more than 0.2 cm and all less than 2 cm in greatest dimension
pNbiii	Extension of tumour beyond node capsule; metastasis less than 2 cm in greatest dimension
pNbiv	Metastasis greater than 2 cm in greatest dimension to a node
pN2	Metastasis to ipsilateral axillary nodes that are fixed to one another or to other structures
pN3	Metastasis to ipsilateral internal mammary nodes
	Distant metastasis (M)
MX	Presence of distant metastasis cannot be assessed
MO	No distant metastases
M1	Distant metastasis (includes metastasis to ipsilateral supraclavicular nodes)

Table 2: Stage Group for Breast Cancer

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

(Source: American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC)1992)

Methods and apparatus in accordance with the invention will now be described with reference to the accompanying drawings, in which:-

- Figure 1 is a schematic diagram of an EIT apparatus;
- Figure 2 shows a cross sectional view of a female human breast;
- Figure 3 shows micro-level equivalent circuits - a) an equivalent circuit of a single cell, b) an equivalent circuit of a group of cells, c) an equivalent circuit of a number of groups of cells;
- Figure 4 shows a) an equivalent circuit of a number of groups of cells, b) the effective equivalent circuit for a number of groups of healthy cells, c) the effective equivalent circuit for a number of groups of diseased cells; and d) an equivalent circuit for a number of circuits of Figure 4(a); and
- Figure 5 shows a micro-range model of a ductal system.

Figure 1 shows EIT apparatus adapted to detect abnormalities in bodily matter 10 comprising:

electrical signal generating means 12 for generating electrical signals at a plurality of frequencies;

an electrode arrangement 14 for applying the electrical signals to the bodily matter 10, and detecting electrically impedance properties of the bodily matter 10; and

data processing means 16, 18, 20 for correlating the detected electrical impedance properties with the presence or absence of abnormalities in the bodily matter 10;

in which electrical signals of a frequency greater than 1MHz, preferably greater than 2MHz, more preferably greater than 3MHz and most preferably greater than 4MHz are applied to the bodily matter.

At these high applied frequencies, differences between normal tissue and abnormal tissue are more pronounced, permitting the detection of abnormalities by EIT. It should be noted that the range of applied frequencies are certainly not restricted to this high frequency range. Indeed, it is preferably to utilise a wider bandwidth - in a representative example, frequencies in the range 1kHz to 5 MHz are applied. Typically a number of spot frequencies across the desired bandwidth are applied, in sequential manner, to the bodily matter. However, it should be noted that the use of time-to-frequency techniques is also within the scope of the invention. In this instance, an appropriate time varying waveform is applied to the electrode arrangement, and the response is monitored as a function of time. The time varying waveform can be considered to comprise electrical signals at a plurality of frequencies. The (time domain) response is then transformed into the frequency domain by an appropriate technique, such as a fast Fourier transform (FFT).

In the present, non-limiting example, the electrical signal generating means 12 comprises a high impedance current source, converting the voltage output of a fully programmable Direct Digital Synthesis (DDS) 50 MHz microchip. An artificial upper limit of 5 MHz is placed on the output frequency, so that the waveform can be synthesised by the DDS chip in ten steps. Higher frequencies might be produced if desired - in principle, a 25 MHz "square" wave can be produced. Current is injected into the electrode arrangement 14, which is of the type well known in the tomographic field, comprising a set of current injection electrodes interlaced with voltage detection electrodes. A 2-dimensional thirty two electrode arrangement (comprising sixteen current injection electrodes and sixteen voltage detection electrodes) and a 1-dimensional four electrode arrangement have been used. The thirty two electrode system provides superior spatial resolution when the electrode systems are of identical dimensions. Detection of the voltage developed at the electrodes is performed using an EIT analogue hardware processing system 16. Data are then digitised by an analogue to digital convertor 18 and transferred to a computer 20 where the data can be stored and processed by a software system base upon commercially available products. The software system firstly collects the raw data from the electrodes and then a signal processing technique is applied to it to remove artefacts such as those caused by electrode-tissue contact problems, EIM system noise and system calibration. A filtered back-projection image method (Prof. David Barker, University of Sheffield) is then used to reconstruct an image. Image analysis is then performed to extract data from the reconstructed image, and the data is then correlated to that in a database containing data for normal and abnormal tissues having been normalised for patient parameters including weight, age and body fat content, and the degree of correlation for the various tissue types determined in order to ascertain the probable nature of the tissue from the sections of the projected data. The software can retrieve data, convert the data to an impedance measure and reconstruct the data to produce a pixelated image.

Although the apparatus and method of the present invention might be used to detect many abnormalities, such as ulcers and thrombosis, a primary example is in the detection of carcinomas. As discussed previously, a particularly important example is the detection of breast carcinomas, more particularly early-stage breast carcinomas.

Figure 2 shows sections through a human breast. Glandular tissue, shown generally at 22, is mainly located under the mammary papilla 24 and areola. The glandular tissue consists of a system of terminal ducts 26 which penetrate deep into the fibroadipose tissue of the breast. Each of the ducts is lined by columnar or cuboidal epithelium, comprising a continuous surface layer of epithelial cells with oval nuclei and an outer discontinuous layer of myoepithelial cells which have clear cytoplasm. The ducts 26 branch into ductules 28 and end in lobes 30. Additionally, there are regions of the breast in the lower and upper quadrants which consist of fat and muscle, and have no underlying glandular tissue. However, these regions are rarely host to any disease. In fact, cancer of the glandular tissue is the most common form of breast disease, of which infiltrating ductal carcinoma comprises 84% and infiltrating lobular carcinoma comprises 10% of all cases.

An important aspect of the present invention is the two-tier fractal or cascaded model of tissue impedance that is used to interpret the EIT measurements. Figure 3a shows a RRC cascade equivalent circuit of a single cell, comprising a series and parallel arrangement of intra-cellular impedance Z_i (111) comprising intra-cellular capacitance C_i (112), intra-cellular resistance S_i (113) and intra-cellular cross-resistance R_i (114); extracellular impedance Z_x (121) comprising extra-cellular fluid capacitance C_x (122), extra-cellular resistance S_x (123) and extra-cellular cross resistance R_x (124); and RRC membrane model Z_m (101) comprising cell membrane capacitance C_m (102), membrane resistance S_m (103) and cross-membrane resistance R_m (104). If, as shown in Figure 3a, this cellular equivalent circuit is denoted by the block "Zcell", then a group of cells can be represented by the circuit shown in Figure 3b, and there may be multiple

cascading levels of this circuit. In this circuit, groups of individual cellular components Z_{cell} are represented by a cascaded arrangement. The equivalent circuit of the combined cells shown in Figure 3b is denoted by the block " Z_{com} ". A still larger volume of tissue can be described by the equivalent circuit shown in Figure 3c, in which the blocks " Z_{com} " are arranged in a different cascaded configuration to that shown in Figure 3b. The process can be repeated to produce equivalent circuits for larger and larger cell groupings.

The fractal model of Figures 3a and 3b are applicable to breast tissue at a "micro" level scale (application to distances of up to about 100 μm), typically representing single cells, basic compound cells/tissue units, and compound tissues. At a "macro" level (applicable to distances in excess of about 100 μm) a different fractal model, namely that of Figures 3b and 4, is appropriate and is capable of representing compound tissues, integral single type cells and integral compound type cells. The exact distances at which the micro and macro models apply will differ slightly from tissue to tissue, and the exact cut-off point for a particular tissue may be readily determined by one skilled in the art. Where the "micro" and "macro" scale fractal models interact (i.e. at approximately 100 μm distances) the Z_{com} units are the same. Thus a "micro" level fractal model Z_{com} unit is used as a "macro" level fractal model Z_{com} unit. This is referred to as the "ICI" model of integrated cell impedance. Thus, the overall model of tissue impedance is a fractal one, in the sense that the equivalent circuit at any give scale comprises sub-units in a common arrangement, and each of the sub-units itself comprises smaller sub-units which are also in the same common arrangement (i.e. the cascaded arrangement of Figures 3 and 4).

The fractal model of tissue impedance takes account of the physiological constitution of the cell/compound tissue/organ/system hierarchy. Furthermore, there is a direct relationship between the fractal model used and the resolution of the EIT system employed - for example, at very high resolution the EIT technique might provide pixels

of data which relate to relatively small groups of cells. This can be equated with the equivalent circuits of Figures 3b and 3c, which might be described as "micro-range" models of tissue impedance. At coarser resolution, the pixels comprising the tomographic image can be related to a "macro-range" model of tissue impedance in which compound tissues such as ductal and lobular structures are modelled, and can be equated with the equivalent circuits of Figure 4. Further still, the fractal model is applicable at the high applied frequencies (i.e. the wide bandwidth) utilised by the present invention. The fractal model can describe all stages of cancer development (0, 1, 2, 3, 4) in the ductal system and the lobular system.

Cancerous tissue gives rise to different electrical characteristics than those exhibited by normal, healthy tissue. Consider the equivalent circuit of the multi-cellular structure shown in Figure 4a. In normal tissue, the potential across the central Zcom block 32 is around 0V. Under these conditions, the multi-cellular impedance can be represented by a single Zcom block, as shown in Figure 4b. As a result, the number of dispersion (or corner) frequencies associated with the tissue will be constant, the ratio of intra and extra-cellular impedance (XIR) and the ratio of extra-cellular and membrane impedance (capacitance), XMR, will be constant.

In contrast, in diseased tissue there is a significantly non-zero potential across the central Zcom block. Under these circumstances, the electrical characteristics, for example dispersion characteristics, will be altered compared to normal tissue. In particular, the diseased tissue exhibits additional dispersions together with changes of XIR and XMR due to variations between the cascaded (parallel) Zcom blocks. Thus, detection of these additional dispersions, XIR and XMR (which might be overlaid) are indicative of the presence of diseased tissue and may be related to changes in the epithelium (degree of disruption of membrane base e.g. ductal/lobular system). Figure 4c shows a representative equivalent circuit, although it should be noted that it may be appropriate to describe the tissue impedance with additional parallel components, such

as that shown in broken lines in Figure 4c. Tables 3 to 5 describe the correlation between detected electrical impedance properties and breast carcinoma pathology.

Table 3a. Matched Pathological/Electrical Parameters for Cancer Detection (in cellular range)

Pathological properties of cancer cells	Electrical Properties of Cancer Cells (non-limiting)
1. Dyskaryosis	Changes and/or large variations of intra-cellular impedance $Z_{i_{com}}$
2. Abnormal nuclear-to-cytoplasmic ratio (NCR)	abnormal $Z_{i_{com}}$, $Z_{x_{com}}$ to $Z_{i_{com}}$ ratio
3. Abnormal inter-cellular cohesion	abnormal $Z_{x_{com}}$
4. Abnormal membrane morphology	abnormal $Z_{m_{com}}$, $C_{m_{com}}$, $Z_{x_{com}} / Z_{m_{com}}$, $Z_{x_{com}} / C_{m_{com}}$, $Z_{m_{com}}$, $Z_{i_{com}}$

Notes:

Z_i - intra-cellular impedance of single cell

$Z_{i_{com}}$ - integral intra-cellular impedance among the cells

Z_x - extra-cellular impedance of single cell

$Z_{x_{com}}$ - integral intra-cellular impedance among the cells

Z_m - membrane impedance of single cell

$Z_{m_{com}}$ - integral membrane impedance among the cells

C_m - membrane capacitance of single cell

$C_{m_{com}}$ - integral membrane capacitance among the cells

Table 3b. Matched Pathological/Electrical Parameters for Cancer Detection (in compound tissue/compound cell range)

Pathological properties of cancer cells	Electrical Properties of Cancer Cells (non-limiting)

Table 4. Matched Pathological/Electrical parameters for Early Stage (non-infiltrate) Cancer Detection

Pathological properties of early stage ductal/lobular cancers	Electrical Properties of the early stage ductal/lobular cancers
1. changes and /or variation of intra-ductal/intra-lobular structures	changes of intra-ductal/intra-lobular impedance $Z_{i_{com}}$ variation of $Z_{i_{com}}$ (dependent on cancer types)
2. changes and /or variation of extra-ductal/extra-lobular structures	changes extra-ductal / extra-lobular impedance $Z_{x_{com}}$
3. changes and /or variation of "basement membrane" of ductal/lobular structure	changes "basement membrane" impedance $Z_{m_{com}}$, $C_{m_{com}}$ (additional dispersion become evident)
4. Abnormal morphology of extra-to-intra relationship of ductal/lobular structure	abnormal extra-to-intra ductal/lobular impedance ratio $Z_{x_{com}} / Z_{i_{com}}$; $Z_{x_{com}} / Z_{m_{com}}$; $Z_{x_{com}} / C_{m_{com}}$

Table 5. Matched Pathological/Electrical parameters for Late Stages (Early-infiltrate and infiltrate stage) Cancer Detection

Pathological properties of Late Stage cancers	Electrical Properties of the Late Stage ductal/ lobular cancers
1. changes and /or variation of intra-ductal/intra-lobular structures	changes of intra-ductal/intra-lobular impedance $Z_{i_{com}}$ variation of $Z_{i_{com}}$ (dependent on cancer types)
2. changes and /or variation of extra-ductal/extra-lobular structures	changes extra-ductal / extra-lobular impedance $Z_{x_{com}}$
3. penetration and /or larger variation of "basement membrane" of ductal/lobular structure	significantly change "basement membrane" impedance and capacitance $Z_{m_{com}}$, $C_{m_{com}}$ (additional dispersions becoming significant)
4. Abnormal morphology of extra-to-intra relationship of ductal/lobular structure	abnormal extra-to-intra ductal/lobular impedance ratio $Z_{x_{com}} / Z_{i_{com}}$; $Z_{x_{com}} / Z_{m_{com}}$; $Z_{x_{com}} / C_{m_{com}}$

In intraductal or in-situ breast cancer, the malignant cells proliferate within the existing ductal system without destruction of the surrounding basement membrane. An example is lobular carcinoma in-situ (LCIS). LCIS is characterised by filling of the lobules with relatively small, uniform cells. Invasive lobular carcinoma has a tendency to spread diffusely between collagen fibres. Figure 5 shows a micro-range model of a ductal system for the detection of early stage ductal carcinoma - a similar model describes lobular carcinoma. In Figure 5, block 50 represents a RRC circuit for ductal basement (epithelial) wall membrane, block 52 represents a RRC circuit for intraductal (integral) impedance including the nucleus and block 54 represents a RRC circuit for extraductal impedance. Block 50 comprises membrane capacitance 56, membrane resistance 58 and cross membrane resistance 60. Block 52 comprises intraductal capacitance 62, intraductal resistance 64 and intraductal cross resistance 66. Block 54 comprises extraductal capacitance 68, extraductal resistance 70 and extraductal cross resistance 72.

In correlating the detected electrical impedance properties with the presence or absence of abnormalities such as carcinomas, it is advantageous to reference the detected impedance properties of the bodily matter to the detected electrical impedance properties of other bodily matter. This referencing procedure might comprise deriving a difference spectrum by subtracting "standard" responses from the measured responses. In the detection of breast carcinomas, it is useful to reference the impedance properties to the detected impedance properties of fatty tissue in the breast, although the referencing might alternatively be with respect to normal gland tissue. A self referencing technique can be employed, in which high impedance fatty areas are masked from the image, followed by normalisation of the remaining data relative to a chosen frequency, such as 1kHz.

In a different approach, higher order differentials (such as second order differentials) of change in impedance are analysed at low and high frequencies and can

give useful information for e.g. tumorous tissues and the surrounding fatty and stroma tissues.

Numerous factors affect the measured impedance properties. An important factor is the temperature at which the measurement is made. This might be accounted for by building the temperature dependence into the correlation step, or preferably, by controlling the temperature at which the measurement is made. When *in vitro* measurements were performed on samples of tissue excised from a breast, it was found that the detected impedance properties vary depending on the orientation of the tissue, i.e. whether the current flow through the tissue is parallel or perpendicular to the excision. An additional factor was the fresh tissue handling procedure used - fresh blood-free tissue ensured a reduction in the unexpected deviation between samples.

Another important factor in the detection of breast carcinomas is the age of the subject. Body size is also important. Both of these factors are linked with body fat and water content. It is possible to account for the variations by compiling a database of impedance properties corresponding to bodily matter of known composition, in particular consisting of measurements made from different subjects, having known breast fat content or, more practically, of known age. The database might comprise a library of such responses, or it might comprise an artificial intelligence system, such as a trained neural network.

In vitro measurements have been performed on a number of breast tissue samples supplied via a clinical collaboration with Glenfield General Hospital, Groby Road, Leicester, UK. Statistically significant differentiation was found between normal and stage 2 and stage 3 infiltrating ductal carcinomas. It has not proved possible to show significant *in vitro* differentiation between stage 1 or earlier cancers and normal tissues at the present time. This has been due, as discussed above, to difficulties in the identification of such carcinomas conventionally, and therefore it is extremely difficult

to obtain sufficient numbers of such samples in the first instance. It is believed that the present invention will be able to detect stage 1 or earlier carcinomas, provided the spatial resolution of the interrogating EIT is commensurate with the small physical dimensions of these earlier stage tumours. This represents a major advantage over X-ray mammography.

It is highly desirable to perform *in vivo* detection since this is non-invasive. One way in which this might be performed in order to detect or screen for breast carcinomas is to dispose at least the electrode arrangement in a woman's brassiere. Such an arrangement can be made comfortable for the subject to wear. Furthermore, by disposing a plurality of electrode arrays in the brassiere, three dimensional images can be produced.

CLAIMS

1. Electrical impedance tomography apparatus adapted to detect abnormalities in bodily matter comprising:

electrical signal generating means for generating electrical signals at a plurality of frequencies;

an electrode arrangement for applying the electrical signals to the bodily matter and detecting electrical impedance properties of the bodily matter; and

data processing means for correlating the detected electrical impedance properties with the presence or absence of abnormalities in the bodily matter;

in which electrical signals of a frequency greater than 1 MHz, preferably greater than 2 MHz, more preferably greater than 3 MHz and most preferably greater than 4 MHz are applied to the bodily matter.

2. Apparatus according to claim 1 adapted to detect a carcinoma.

3. Apparatus according to claim 2 adapted to detect a breast carcinoma.

4. Apparatus according to claim 2 or claim 3 adapted to detect a stage 3 carcinoma.

5. Apparatus according to any of claims 2 to 4 adapted to detect a stage 2 carcinoma.

6. Apparatus according to any of claims 2 to 5 adapted to detect a stage 1 carcinoma.
7. Apparatus according to any previous claims in which the data processing means correlates the detected electrical impedance properties with the presence or absence of abnormalities using a fractal model of tissue impedance.
8. Apparatus according to any previous claim in which information related to dispersion frequencies is used to perform the correlation.
9. Apparatus according to any previous claims in which the ratio of intra cellular impedance and extra cellular impedance is used to perform the correlation.
10. Apparatus according to any previous claims in which the data processing means references the detected electrical impedance properties of the bodily matter to the detected electrical impedance properties of other bodily matter.
11. Apparatus according to claim 10 when dependent on claim 3 in which the impedance properties are referenced to detected electrical impedance properties of fatty tissue in the breast.
12. Apparatus according to previous claim in which the data processing means is adapted to compare the detected electrical impedance properties with a database of impedance properties corresponding to bodily matter of known compositions.
13. Apparatus according to claim 12 in which the database comprises impedance properties of bodily matter obtained from subjects of differing and known ages.

14. Apparatus according to any previous claims in which at least the electrode arrangement is disposed in a women's brassiere.

15. An electrical tomographic method for detecting abnormalities in bodily matter comprising the steps of:

generating electrical signals at a plurality of frequencies;

applying said electrical signals to the bodily matter;

detecting electrical impedance properties of the bodily matter; and

correlating the detected impedance properties with the presence or absence of abnormalities in the bodily matter;

in which electrical signals of a frequency greater than 1 MHz, preferably greater than 2 MHz, more preferably greater than 3 MHz and most preferably greater than 4 MHz are applied to the bodily matter.

16. A method according to claim 15 in which the abnormality is a carcinoma.

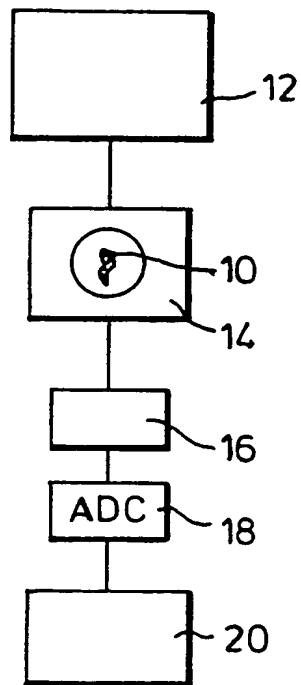
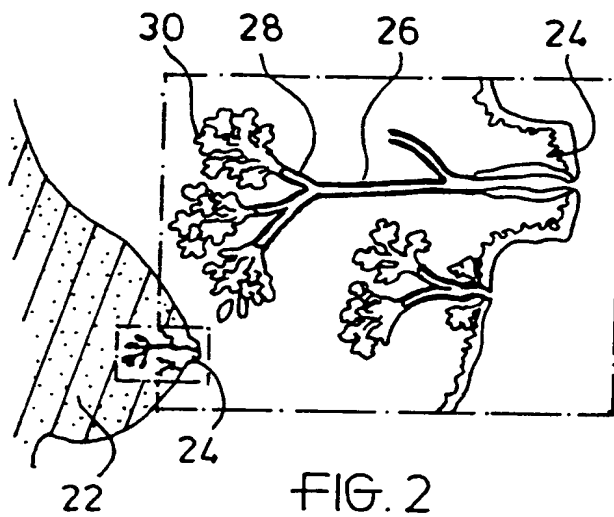
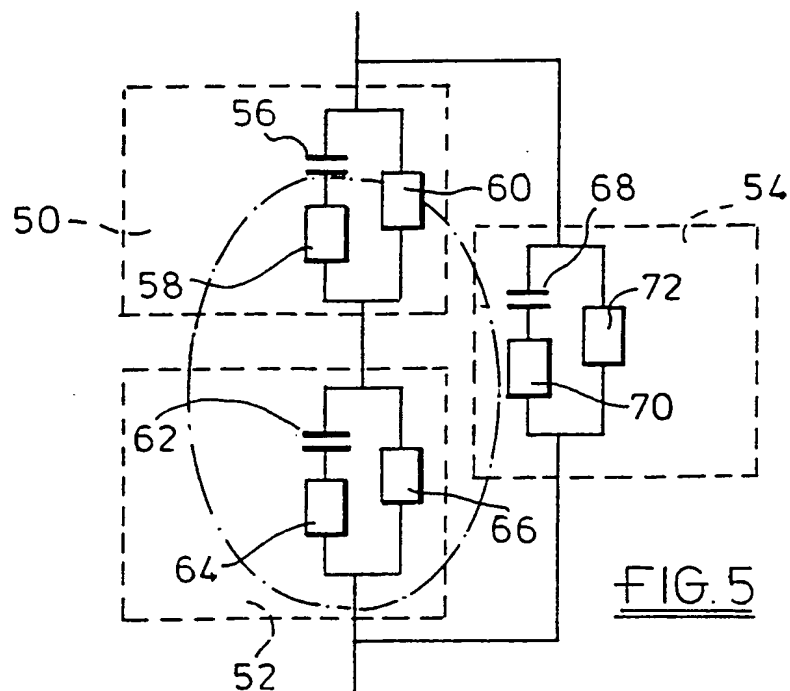
17. A method according to claim 16 in which the abnormality is a breast carcinoma.

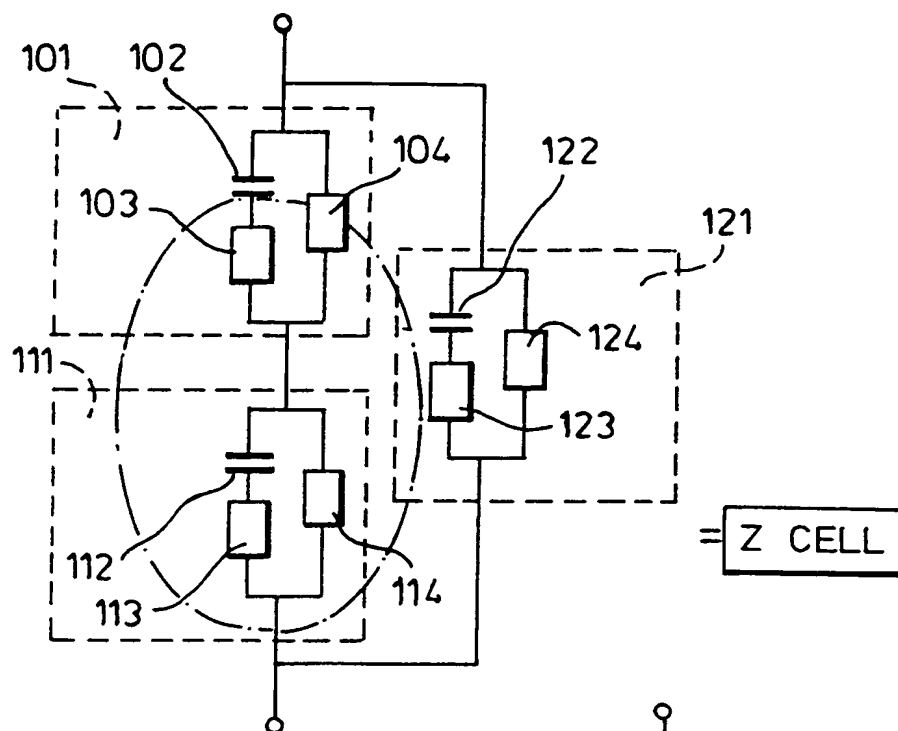
18. A method according to claim 16 or claim 17 in which a stage 3 carcinoma is detected.

19. A method according to any of claim 16 to 18 in which a stage 2 carcinoma is detected.
20. A method according to any of claims 16 to 19 in which a stage 1 carcinoma is detected.
21. A method according to any of claims 15 to 20 in which the correlation of the detected impedance properties with the presence of absence of abnormalities uses a fractal model of tissue impedance.
22. A method according to any of claims 15 to 21 in which information related to dispersion frequencies is used to perform the correlation.
23. A method according to any of claims 15 to 22 in which the ratio of intra-cellular impedance and extra-cellular impedance is used to perform the correlation.
24. A method according to any of claims 15 to 23 in which the detected electrical impedance properties of the bodily matter are referenced to detected electrical impedance properties of other bodily matter.
25. A method according to claim 24 when dependent on claim 17 in which the impedance properties are referenced to detected electrical impedance properties of fatty tissue in the breast.
26. A method according to any of claim 15 to 25 in which the detected electrical impedance properties are compared with a database of impedance properties corresponding to bodily matter of known composition.

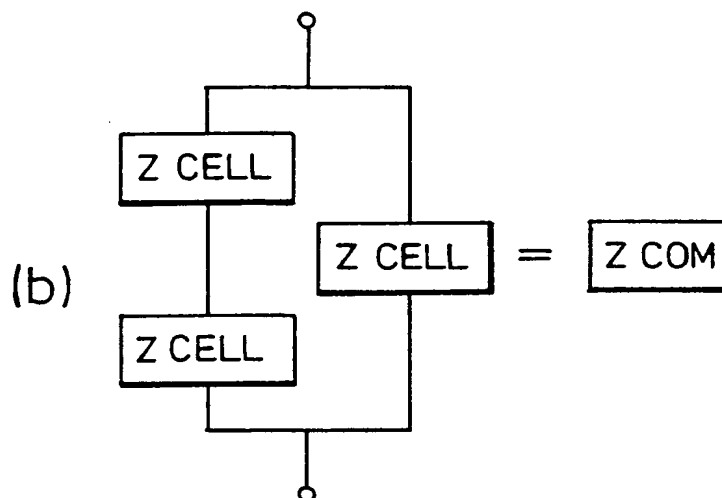
27. A method according to claim 26 in which the database comprises impedance properties of bodily matter obtained from subject of differing and known ages.

28. A method according to any of claims 24 to 27 in which the the detected electrical impedance properties of the bodily matter are referenced or compared to impedance properties of other bodily matter of a controlled temperature.

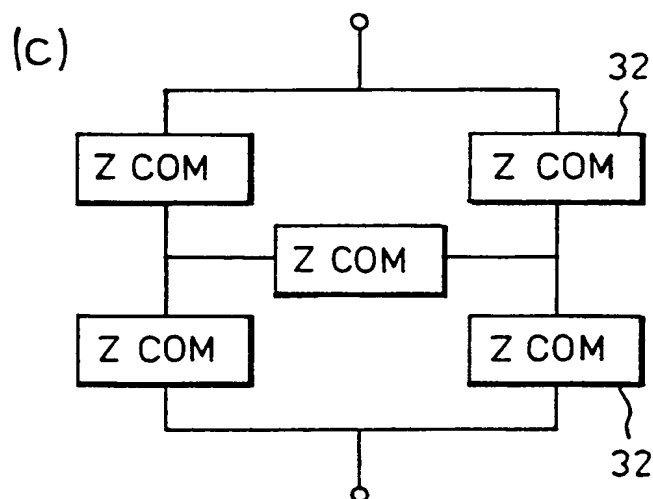
FIG. 1FIG. 2FIG. 5



(a)

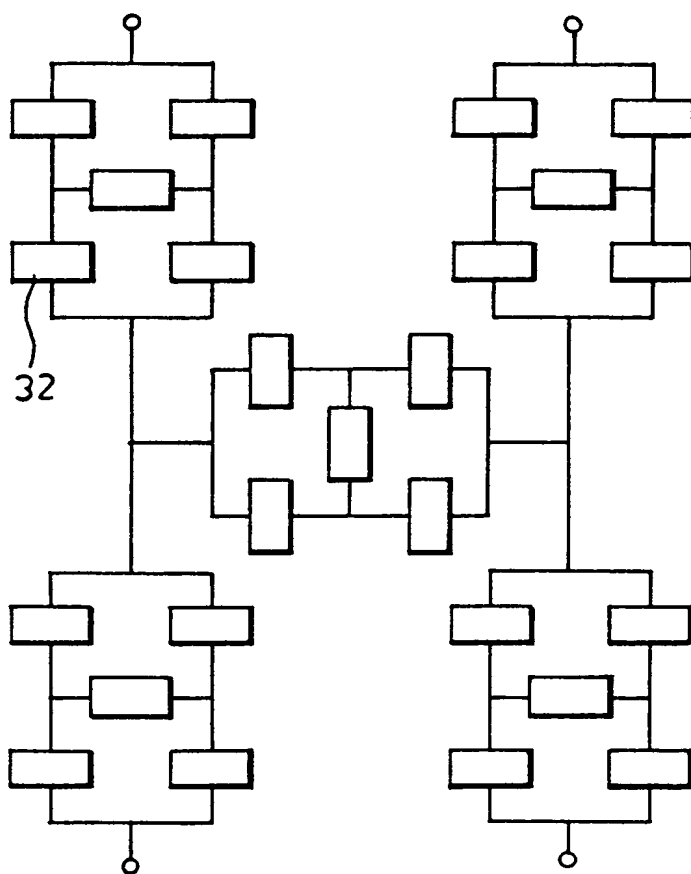
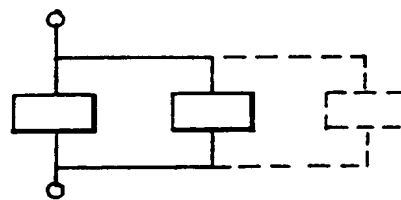
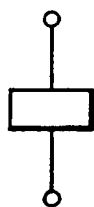
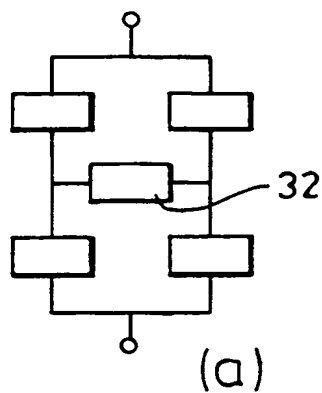


(b)



(c)

FIG. 3



(d)

FIG. 4

INTERNATIONAL SEARCH REPORT

National Application No

PCT/GB 98/02952

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOSSINET J: "VARIABILITY OF IMPEDIVITY IN NORMAL AND PATHOLOGICAL BREAST TISSUE" MEDICAL AND BIOLOGICAL ENGINEERING AND COMPUTING, vol. 34, no. 5, September 1996, pages 346-350, XP000626980	1-3,7,8, 15-17,22
A	see abstract see whole article ---	9-13, 21-26 -/--



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

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08/04/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/02952

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MURARI KEJARIWAL ET AL: "BREAST CANCER DETECTION USING ELECTRICAL IMPEDANCE TOMOGRAPHY: SPICE SIMULATION" VISUALIZATION, IMAGING, SIGNAL PROCESSING, MODELING, NEURAL NETWORK, SAN DIEGO, OCT. 28 - 31, 1993, vol. 1, no. CONF. 15, 28 October 1993, page 64/65 XP000436658 SZETO A; RANGARAJ M RANGAYYAN see abstract see whole article ---	1-3, 15-17
X	RIU P J ET AL: "MULTI-FREQUENCY STATIC IMAGING IN ELECTRICAL IMPEDANCE TOMOGRAPHY PART 1: INSTRUMENTATION REQUIREMENTS" MEDICAL AND BIOLOGICAL ENGINEERING AND COMPUTING, vol. 33, no. 6, 1 November 1995, pages 784-792, XP000540711 see abstract see page 784, left-hand column, line 1 - page 787, left-hand column, line 32; tables 1-5 ---	1, 15
A	US 5 704 355 A (BRIDGES JACK E) 6 January 1998 see column 3, line 19 - column 4, line 67; tables 1, 2 ---	1-3, 15-17
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